

## Review of dry powder inhalers

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### Abstract

The search for alternatives to metered-dose inhalers has accelerated recently in a bid to find effective products that do not use chlorofluorocarbon (CFC) propellants. This paper reviews the factors to be considered in developing dry powder inhalers (DPIs), particularly the formulation, metering design and flow path in the device. The advantages and disadvantages of current DPIs are discussed and possible future approaches outlined. © 1997 Elsevier Science B.V.

**Keywords:** Dry powder inhalers; Chlorofluorocarbon propellants; Inhalation device; Device design; Dose delivery

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### 1. Introduction

Inhalation drug delivery has been used for many years for the delivery of pharmacologically active agents to treat respiratory disease. Traditional asthma therapy with bronchodilators, steroids, mast cell stabilizers, and anticholinergic drugs has primarily used the pressurized metered-dose inhaler (MDI). However, this delivery system is now under increasing threat because of the environmental concerns regarding chlorofluorocarbon (CFC) propellants. A

range of alternative devices, such as dry powder inhalers, which do not contain propellants are being evaluated and developed. This article covers the development of dry powder inhalers, including the design of the formulation, metering system and flow path. The advantages and disadvantages of some design options (summarised in Fig. 1) are discussed.

Powder inhalers are versatile delivery systems which may require some degree of dexterity to operate, although one of the objectives of recent developments has been to simplify their operation. Typically, they dispense a metered quantity of powder in a stream of air drawn through the device by the patients own inspiration. In the design of a

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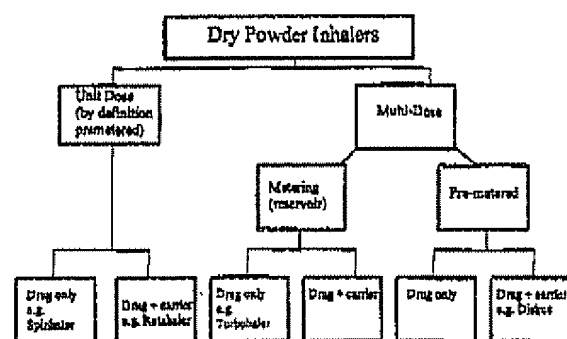


Fig. 1. Types of dry powder inhalers.

new powder inhaler consideration must be given to optimising the formulation of the powder containing the drug substance to ensure a chemically stable and consistent dose; design of the metering system within the inhaler to provide consistent doses over a range of inhalation conditions; and design of the powder inhaler itself to produce a convenient device that is comfortable and easy for the patient to use.

Inasmuch as these devices do not require CFC propellants to disperse the drug, they can be regarded as ozone-friendly delivery systems. However, concerns that they will not be able to totally replace MDIs due to limitations of dose delivered and flow rates achieved through the devices for severely diseased patients are probably valid [1], based on the capabilities of currently available powder inhalers. Vidgren et al. [2] have shown different deposition patterns in healthy volunteers from the same formulation in four single-dose DPIs. Newman et al. [3] have also shown different in-vivo deposition patterns in healthy volunteers using Turbuhaler inhalers operated at optimal and sub-optimal peak inspiratory flow rates. Clearly, some current designs of DPIs are subject to variations in performance due to differences in inhalation flow rates. Future designs may require that the dispersion of the powder dose be independent of patient inhalation.

## 2. Formulation design

Of critical importance in the development of powder inhalation products is the optimization and control of flow and dispersion (deaggregation) characteristics of the formulation (see K. Johnson, Wen-Li Li and David Edwards, this issue). These

properties are a function of the principal adhesive forces between particles, including Van der Waals forces, electrostatic forces and the surface tension of absorbed liquid layers [5]. The forces are influenced by several fundamental physicochemical properties, including particle density and size distribution, particle morphology (shape, habit, surface texture) and surface composition (including absorbed moisture) [6].

Interparticle forces that influence flow and dispersion properties are particularly dominant in the micronised or microcrystalline powders that are required for inhalation therapy (particles smaller than 5  $\mu\text{m}$ ). Bulk drug modifications, both chemical and physical, have been attempted in order to enhance respirable dose performance. In one study [7], spray-dried salbutamol sulfate was seen to perform as well as micronised material. In the case of sodium cromoglycate, several approaches have been successfully employed to improve flow and dispersion characteristics, including controlled aggregation of the undiluted drug to form loosely adherent flocs [8,9]. This approach takes advantage of the inherent cohesiveness of the particles.

To minimize hygroscopic growth, lipophilic coating materials have been investigated using disodium cromoglycate [6]. In addition, crystals of the parent acid and the effects of aspect ratios (longest and shortest dimensions) have been studied [10]. Vidgren et al. [11] have shown that spray-dried particles of disodium cromoglycate have better (at least in vitro) aerodynamic properties (a higher fraction of dose in a smaller size range) than micronised material.

Other techniques for modifying drug characteristics have been discussed, such as recrystallisation from supercritical fluids [12].

A DPI formulation may consist of drug alone, or of drug blended with a carrier material (which is usually lactose).

Blending the drug with a carrier has a number of potential advantages, such as increasing the bulk of the formulation. This allows easier metering of small quantities (typically < 100  $\mu\text{g}$ ) of potent drugs, either at the manufacturing stage (if the doses are pre-metered) or within the device itself for a reservoir device. Provided that content uniformity of the blend is well controlled, this approach can improve the subsequent dosing consistency of the inhaler. The presence of the carrier material, in separating the

very fine drug particles, can also improve processing (e.g. flow characteristics) of the formulation. The carrier properties (particle size distribution, particle surface characteristics) can be used to influence/control fine particle mass.

—An additional benefit that may be gained from the use of a carrier such as lactose is the taste/sensation on inhaling, which can assure the patient that a dose has been taken. Clearly, the influence of the carrier material on product stability must be carefully assessed, and the range of materials available for use as carriers in inhaled products is limited for toxicological reasons. Lactose and other sugars have been studied and used, and modifications to these materials may allow further formulation optimisation. Modifications to the lactose surface have been proposed that would improve the surface characteristics (reduce the rugosity) of the material. Ganderton [13] claims that reducing the rugosity increases the percentage of respirable particles in conventional powder inhalers.

### 3. Metering design

Whether a drug only or a drug-carrier system is adopted, a key decision in the design of a DPI is whether to use a factory metered dose or to include a reservoir and metering mechanism in the device itself.

Early popular DPIs utilised factory-metered doses. Conventional capsule-filling technology, already well established in the early 1970s, was used to manufacture unit doses that could be inhaled from relatively simple devices.

The concept of the Spinhaler was first described in the early 1970s by Bell et al. [8] who had developed this device for the administration of powdered sodium cromoglycate. Typically, the drug mixture, which often includes a bulk carrier to aid powder flow (most notably lactose), is pre-filled into a hard gelatin capsule and loaded into the device. Following activation, where the capsule is pierced, the patient inhales the dose, which is dispensed from the vibrating capsule by means of inspired air. A similar device (Rotahaler, Glaxo Wellcome) has been developed for the delivery of salbutamol and beclomethasone dipropionate powders. Here, the drug mixture is again filled into a hard capsule and the

capsule is inserted into the device, wherein, it is broken open and the powder inhaled through a screened tube [14]. Other devices dispense drug loaded into hard gelatin capsules; these include the Berotec (Boehringer Ingelheim) used for fenoterol [15].

These devices have performed well in clinical use for almost 20 years. Their primary disadvantage is the cumbersome nature of loading, which may not be easily accomplished if a patient is undergoing an asthma attack and requires immediate relief.

The development of multidose dry powder inhalers has been pioneered by A.B. Draco (a Division of Astra) with their Turbuhaler [16] and by Glaxo Wellcome with the introduction of the Diskhaler [17] and recently the Diskus [18]. The Turbuhaler device is a reservoir-based powder inhaler. The drug is contained within a storage reservoir and can be dispensed into the dosing chamber by a simple back-and-forth twisting action on the base of the unit. The device delivers carrier-free particles of both the  $\beta$ -agonist, terbutaline sulfate, as well as the steroid, budesonide [19].

The Diskhaler (Glaxo Wellcome) has been introduced for the delivery of both the short-acting  $\beta$ -agonist, salbutamol, as well as the longer-acting, salmeterol [20]. In addition, the steroids beclomethasone dipropionate and fluticasone propionate are available in disks. These devices have a circular disk that contains a number of powder charges (four or eight), depending on a typical dosing schedule. The doses are maintained in separate aluminum blister reservoirs until just prior to inspiration, thus ensuring the integrity of the powder blend against moisture ingress. On priming the device, the aluminum blister is pierced and the powder charge is dropped into the dosing chamber.

The Diskus device represents a further development of the Diskhaler approach, with the pre-metered doses sealed in blisters on a foil strip. Use of a coiled strip, rather than a disk, allows 60 doses of medication to be contained within the device.

There are two main advantages in the use of a pre-metered dose. Firstly, the precision with which the dose can be metered in the factory is superior to the typical precision of metering that can be achieved within a device alone, as required by a reservoir-based powder inhaler. With an efficient delivery system, the enhanced precision of metering will

## Frequency Distribution of doses delivered at 60 l/min

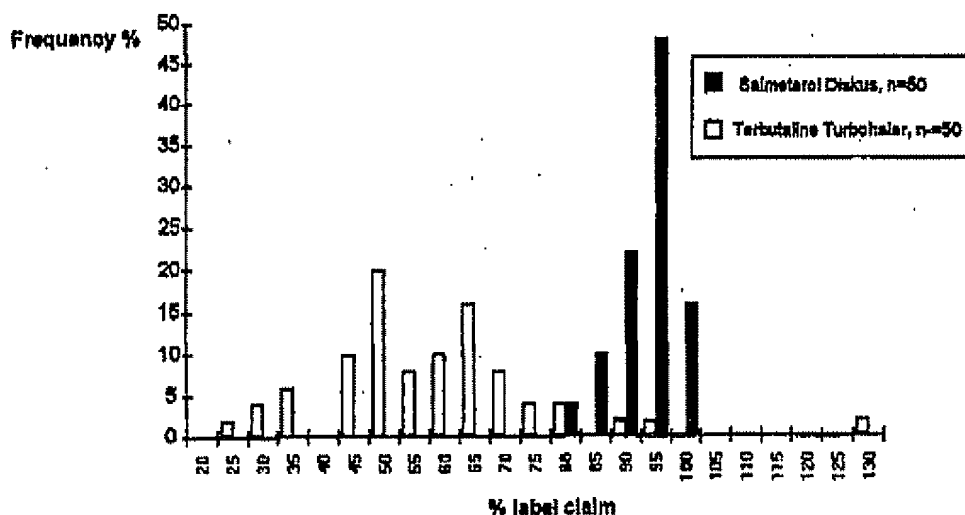


Fig. 2. From Malton et al. [21].

result in improved consistency of the delivered dose. Fig. 2 illustrates this point. The graph shows the frequency distribution of doses delivered at 60 l/min from a terbutaline Turbuhaler and a salmeterol Diskus [21]. The pre-metered doses from the Diskus device are more consistent than the doses delivered from the reservoir device.

Secondly, the pre-metered doses can be individually sealed and protected from the environment until the point of use by the patient. Brindley et al. [20] have shown that the drug content per blister and the dose delivered at 60 l/min from the salmeterol Diskus device is unaffected by storage at high

humidity. These results are reproduced in Table 1. A reservoir that contains all of the doses may be more susceptible to deterioration through ingress of moisture. Some Turbuhaler products are designed to contain a desiccant within the device, to reduce the effects of moisture uptake, although Meakin [22,23] has demonstrated limitations to this approach.

The advantages of the reservoir/metering device approach are the relative ease and cost of manufacture, since these devices can be 'dump' filled with very high manufacturing throughput. A further advantage of the reservoir approach is the relative ease of including a large number of doses within the

Table 1  
Summary of stability data for three batches of salmeterol Diskus (50 µg/blister) stored at high humidity [20]

Storage conditions	Batch 1	Batch 2	Batch 3
(A) Mean content of salmeterol per blister (% of label claim)			
Initial	97.9	100.2	101.0
24 months, 25°C/60% RH	96.2	99.8	97.5
1 month, 40°C/75% RH	100.1	100.1	99.8
(B) Mean salmeterol content of the delivered dose at 60 l/min (µg)			
Initial	45.3	46.5	44.9
24 months, 25°C/60% RH	45.8	50.2	46.1
1 month, 40°C/75% RH	45.8	47.7	46.4

RH = relative humidity.

device. Newman [24] has also shown that the Turbuhaler inhaler performance in-vivo compares favourably with pressurised metered dose inhalers.

#### 4. Manufacturing design

When the DPI design moves away from the more simple gelatin capsule technology of inhalers such as the Spinhaler, considerations have to be given to the complex design of the device itself and to the development of the specialist equipment necessary to manufacture the device components and to fill and assemble the final product. For example, Brindley et al. [20] describe the complex procedure involved in producing a multi-dose foil blister strip and packaging it in the Diskus device, together with the in-process controls carried out to ensure the quality of the product. Wetterlin [16] also describes the complex structure of the Turbuhaler device. Brown [25] outlines the complex processes involved in developing a new dry powder formulation at the same time as designing a new inhaler suitable for dispensing the formulation. He draws attention to the necessity of developing toxicological testing procedures that are relevant to the final product. Advanced in-vitro testing techniques are also required to estimate more accurately the performance of a DPI in clinical use. Clearly, the more recent developments in DPI technology necessitate a large resource input for the development and manufacture of the devices themselves, as well as more detailed testing procedures to ensure the optimum drug delivery from these inhalers.

#### 5. Flow path design

In combination with the design of the formulation and the approach to metering, the third critical factor that determines product performance is the flow path of the device, particularly between the exposed dose to be inhaled and the exit of the mouthpiece. An ideal flow path design would allow efficient and consistent emptying of the device across a wide range of flow rates, with sufficient turbulence to disperse/deaggregate the powder and thereby provide an effective 'lung dose'.

The flow path of the Diskus device is extremely

short, with the powder passing through a single 'crucifix' grid to generate the necessary turbulence. As a result of the short flow path, drug losses within the device are minimised, allowing approximately 90% of the metered dose to be delivered. The Turbuhaler typically delivers only 60% of the metered dose, presumably due to greater drug losses within the device [26].

The flow path of the Turbuhaler was carefully designed to maximise turbulence, using a long flow path with spiral channels in order to generate shear forces that would disperse the drug aggregate and produce a good fine particle mass [16]. At 60 l/min, the Turbuhaler can produce up to 50% of the emitted dose as respirable particles ( $< 5 \mu\text{m}$ ), although the percentage is considerably reduced at lower flow rates [27].

A further disadvantage of a long flow path is a potential increase in the device's resistance. The higher the resistance of the device, the greater the effort a patient has to make in order to achieve a given flow rate [28]. The flow rate achieved may be important in determining the performance of the device [29]. With careful flow path design, and the use of a lactose carrier, some devices such as the Diskus, are relatively insensitive to flow rate and deliver a consistent dose over a wide range of inhalation conditions [30]. Device resistance can also affect the patient's comfort in using the inhaler. De Boer et al. [31] established that an increase in peak inspiratory flow rate is obtained with decreasing inhaler resistance and that, in healthy volunteers, on average, 55% of maximum effort was regarded as comfortable.

Fig. 3 [21] compares the dose delivered from the Diskus and Turbuhaler inhalers at a range of flow rates. The inhaler resistances at each flow rate are also shown in the figure and indicate that the Turbuhaler has a higher resistance than the Diskus inhaler. The graph also shows that the Turbuhaler delivers a smaller proportion of each dose than the Diskus and is more dependent on flow rate.

#### 6. Functional design

Although separate from product performance, the patient-related features of the device are also an integral part of the design. Ease of use is the most

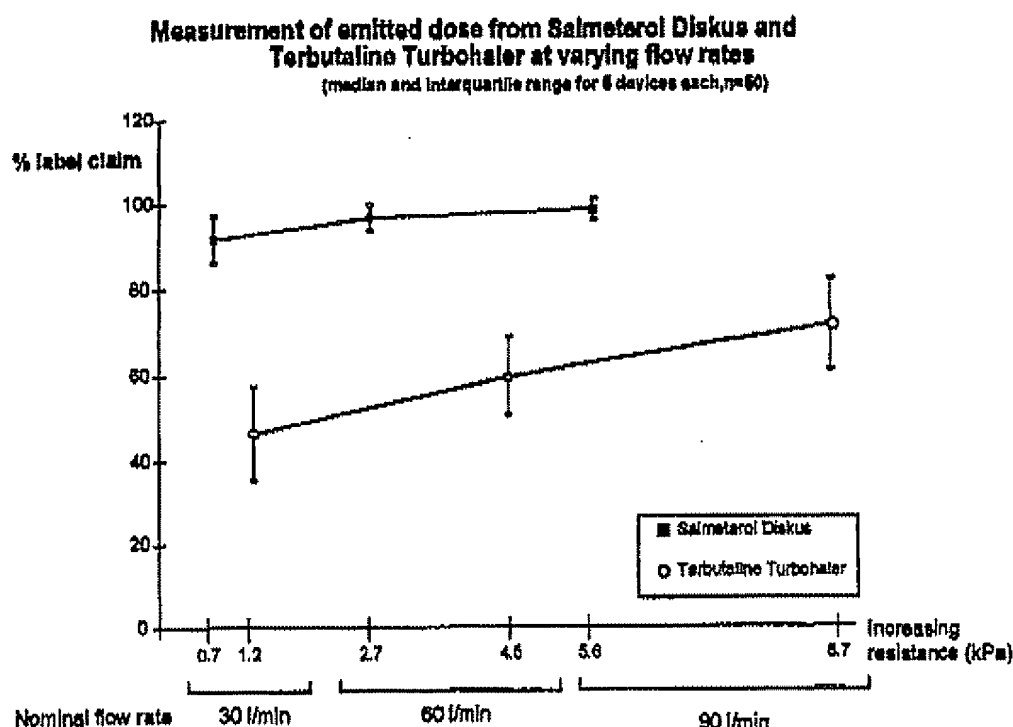


Fig. 3. Comparison of the dose from Diskus and Turbuhaler inhalers at various flow rates [21].

fundamental aspect, particularly for old or very young patients where manual dexterity may be limited. Increasingly, however, additional features will be expected in modern devices, such as an accurate dose counter, integral cover (if necessary to protect the mouthpiece), a locking mechanism to indicate that the labelled number of doses have been used, an indicator to show that a dose has been correctly taken, etc. Additionally, it is important to design the inhaler such that misuse of the device cannot easily result in large overdoses of drug being inhaled or in device failure.

## 7. Novel inhalation delivery systems

Interest in the design of more compact portable inhalation delivery systems is increasing. The patent literature offers numerous examples of applications for novel delivery systems that purport to be potential replacements for the pressurized MDIs, and much is being published in this field [32,33]. Consideration is being given to delivery of biotherapeutic

materials, such as some proteins and peptides, by inhalation aerosol [34].

A number of potential new devices are emerging in the powder area, ranging from simple unit-dose devices to more complex multidose systems [35]. In addition, true breath-activated systems, coupled with an auxiliary means for dispersion of the metered powder [36] hold much promise for the future, if they can pass the trials of converting a sound laboratory principle into a commercially successful device. This, of course, will take several years and may well be driven by patients' needs and the acceptability of alternatives to the widely used MDI.

## 8. Summary

Common to all inhalation dosage forms and delivery systems is the need to generate the optimum 'respirable dose' (particles with aerodynamic diameters  $< 5.0 \mu\text{m}$ ) of a therapeutic agent consistently and reliably. This is a key performance feature in the rational design and selection of a delivery system.

Moreover, this performance, in terms of aerosol quality, should be demonstrated throughout the product's shelf life, in addition to the more usual chemical and physical stability criteria. When considering these delivery systems, it is important that the device design and formulation work have been integrated in the overall design and development of the product. Frequently, therefore, such inhalation delivery systems tend to be compound or company specific.

In summary, in the short term, suitable replacements for pressurized metered dose inhalers (be they powder or liquid based) are unlikely, but if some of the systems that are currently being developed are able to achieve the convenience and compactness of the MDI and have similar (or improved) pharmaceutical performance, they might be in widespread use in the latter part of the decade.

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